REMARKS

Claims 56-78 are presently pending. Claim 56 and 60 are amended herein, as described more fully below. Claim 63 is cancelled herein, as the subject matter recited therein is already recited in claim 60 from which it depends. Claims 71-73 are amended to correctly state the dependencies thereof. Claim 78 is amended for clarity.

The withdrawal of the prior rejection under 35 U.S.C. §112 is noted with appreciation.

The present invention relates to an apparatus and method for the anaerobic proliferation and delivery of cells, tissue culture, or microorganisms, in which the cells, tissue culture, or microorganisms are maintained in an anaerobic chamber, and provided with an inoculum to promote proliferation while the anaerobic environment is maintained. In accordance with the invention, the apparatus comprises an anaerobic proliferation chamber, an inoculation chamber, an openable separator between the chambers, and a means for opening the openable separator to allow the inoculum to inoculate the matter in the proliferation chamber at such time as is desired by the user thereof. The apparatus and method are relatively simple to use even by a novice end user and do not require expertise in microbiology technique, because the features of the apparatus and the steps of the method are such that the risk of contaminating the microorganisms with unwanted microorganisms and the risk of oxygen ingress are significantly reduced through the use of the present invention.

The rejection of claims 56-64 and 71-78 as obvious over Kertz (WO 90/15527) under 35 U.S.C. §103 is respectfully traversed.

The Kertz reference discloses an apparatus in the form of an "integument." The integument is made of a gas-permeable outer membrane and includes one or more internal containers. The inner containers are breakable from the outside of the integument, and are made of a material that is designed to burst under pressure applied from the exterior to release the contents thereof into the interior of the integument (p. 11, second paragraph). It will be appreciated that the inner containers may break inadvertently or uncontrollably if unintended pressure is applied, such as during storage or transport of the apparatus.

Such inadvertent breakage is highly undesirable, especially if the contents are anaerobic cells, tissue cultures, or microorganisms, as is the case in the present invention. In the field of

the present invention, generally only a limited period of time is available to dispense the contents of the inoculation chamber into the proliferation chamber, mix the contents, allow proliferation, and then deliver the contents of the proliferation chamber. Release of the contents of the inoculation chamber and mixing of the contents must both take place under supervision. Uncontrolled release of the inoculation chamber contents into the proliferation chamber, as is possible with the apparatus of Kertz, could reneder the contents of the proliferation chamber unusable

This is different from the apparatus and method of the present application, which relates to a method and apparatus wherein the inoculation chamber is exterior of a proliferation chamber. When it is desired to add the contents of one chamber to that of the other, a separator disposed between the chambers is opened by a user operating an opening means. It will be appreciated that it is virtually impossible for the opening means to open the separator unless deliberate action is taken to use the opening means against the separator, such that it is not possible for the contents of the two containers to accidentally mix.

Independent claim 56 and 60 are amended herein to recite that the inoculation chamber is exterior of the proliferation chamber. Because of this arrangement, it is impossible for the contents of the two containers to accidentally mix if one of the two containers is inadvertently broken or otherwise compromised. Such an arrangement also allows the proliferation and inoculation chambers to be stored and transported separately from one another, if desired, so that it would be physically impossible for the contents of the two chambers to be mixed inadvertently.

Further, claims 56 and 60 each contain the limitation that the step of opening the separating means takes place without compromising the anaerobiosis of the inside of the chambers, and that the steps of disposing, storing, inoculating, opening, and proliferation take place under anaerobic and aseptical conditions. Thus, in the apparatus and method of the present claims the chambers are sealed to be totally airtight and to protect the interior of the chambers from each other and from the outside environment. This is possible because of the physical separation between the two chambers as recited in the claims as amended. This arrangement is superior to the arrangement disclosed in Kertz. In Kertz the inoculation chamber is disposed in the interior of the proliferation chamber, with the contents of the proliferation chamber in direct contact with the exterior surface of the inoculation chamber. This arrangement poses a risk of

contamination of the contents of the proliferation chamber. Kertz does not disclose an apparatus or method wherein the steps of disposing the ingredients into the chambers, storing, inoculating, opening, and proliferating all take place anaerobically.

Yet another advantage of the present invention is that by totally enclosing and hermetically sealing the chambers of the apparatus of the present invention, the apparatus is totally sealed and the proliferation chamber is thus able to expand under the pressure that builds up as a result of the anaerobic cultivation of the microorganisms.

The following discussion will address the points raised in the lettered subparagraphs of paragraph 5 at pages 2-7 of the Office Action.

(a) At page 15, second paragraph, the Kertz reference states "The cellule 30 [i.e., the outer chamber 31, see p. 8, paragraph 1] for culturing these microorganisms can be made form less permeable materials so as to preclude a gaseous interchange between the ambient environment and the organic material." First, it is noted that the walls of the chamber are described as "*less* permeable" (emphasis added) but are never described as being totally gas impermeable so as to form a hermetic seal. Moreover there is no teaching or suggestion that the walls that form the inoculation chamber(s) also should be anaerobic, i.e., formed of a material that does not allow the passage of the air to the inoculum prior to the addition of the inoculum to the proliferation chamber, as recited in the present claims.

In fact Kertz teaches the express opposite. At page 20, lines 9-14, Kertz teaches "In most applications, the inner containers [i.e., the containers that house the inoculum] do not house a growing plant or organism, and therefore *gas permeability is not a concern*. In general, the inner containers only need to have the property of liquid impermeability, in that they will house liquids." [Emphasis added.] Thus Kertz specifically teaches away from the claim limitation that the inoculation chamber be anaerobic. Specifically with respect to the comment at page 3, lines 9-11 of the Action, Kertz teaches at page 8 paragraph 1 and page 20 paragraph 2 that the cellule 30 that surrounds the inoculation chamber [i.e., the proliferation chamber] can be anaerobic, but does not teach that the inoculation chamber is anaerobic, as recited in the present claims. Moreover, since in Kertz the inoculation chamber is interior of the proliferation chamber, there would be no reason for the inoculation chamber to be anaerobic if the proliferation chamber is anaerobic. In the presently amended claims, the inoculation chamber is exterior to the

proliferation chamber. Thus the inoculation chamber also must be anaerobic as presently recited. This feature of the present invention is thus not taught or suggested by the disclosure of Kertz.

Contrary to the Action, the Kertz reference teaches nothing about anaerobic conditions at any of page 20 paragraph 2, page 11 paragraph 2 – page 12 paragraph 3, or page 4 paragraph 3. As noted, page 15 paragraph 2 relates only to a material being "less permeable," not *impermeable*, and in any event relates only to the walls of the proliferation chamber, not the inoculation chamber.

The discussion at pages 9-10 makes evident that the Kertz apparatus is designed for aerobic conditions. As stated therein, "In particular, it is important to achieve optimum gas exchange and light transmission to permit the necessary biochemical activity conducive to life. The membrane 12 must readily pass oxygen from the atmosphere into the chamber 31 of the integument 10 to be diffused through the contents thereof for us by the organic material in metabolic processes and also pass carbon dioxide out of the chamber 31 of integument 10. Thus the membrane 12 of integument 10 is made of a semi-permeable and translucent material which permits gas transfer therethrough, described in detail below." Kertz clearly contemplates aerobic chambers with gas-permeable walls.

Further contrary to the Action, Kertz does not disclose that materials can be added to the chambers through the use of a tube after the chambers are *sealed*. At page 10, paragraph 3, Kertz discloses that "the contents are inserted through an opening 28 into the chamber 31 of integument 10. Thereafter, the opening 28 may be heat sealed at 36 for closing the chamber 31 of integument 10. If desired, a means may be provided, such as a tube, for introducing material to the integument 10 after the same has been *filled*." Thus Kertz teaches the use of a tube to add materials to a chamber after it has been *filled*, but does not teach how to do so after it has been *sealed*. Significantly, there is no illustration in Kertz of a tube being used to fill a sealed container. Nor is there any discussion of how to use a tube to add material to a sealed container while maintaining the anaerobic conditions recited in the present claims.

Nor does Kertz disclose a separator between the chambers, as recited in claim 56. At page 11 paragraph 2 – page 12 paragraph 1 of Kertz, cited in the action, there is disclosed the fact that the an inner chamber can be burst by pressure applied by a flat edge. This flat edge is not a separator, nor is the wall of the inner chamber a "separator" in the sense of claim 56, wherein the "separator" is an element recited as being distinct from the walls of the chambers.

In sum, even if it would have been obvious to one of ordinary skill in the art to perform all the methods steps of claim 56 anaerobically, which it was not, it would not have been obvious to perform all those steps anaerobically by the method recited in claim 56, namely, with all chambers maintained under anaerobic conditions, with each and every step performed under anaerobic conditions, with the inoculation chamber being exterior of the proliferation chamber to prevent accidental contamination of the proliferation medium with the inoculum, and with a separator element being distinct from the chamber walls. Thus claim 56 is not obvious under 35 USC 103.

(b) Claim 57 recites that "the inoculum is provided in a form which is stable and viable beyond the normal life-span of a conventional culture in a closed container." The Kertz reference teaches at page 31 paragraph 3 teaches only that the contents are sterile, but teaches nothing about the stability or viability of the contents, and in particular teaches nothing about the stability or viability of the contents relative to the normal life-span that would be experienced in conventional culture in a closed container. Accordingly Kertz does not render claim 57 obvious under 35 U.S.C. §103.

(c) Claim 58 recites the step of "rendering the separating means and inside of the proliferation chamber sterile…." As noted above, Kertz does not teach a separating means as a distinct element as recited in the present claims, therefore Kertz cannot teach rendering such a separating means sterile, and claim 58 is not rendered obvious by Kertz under 35 U.S.C. §103.

(d) Claim 59 is non-obvious as depending from a non-obvious base claim.

(e) As to claim 60, as noted above Kertz does not teach or suggest that the inoculation chamber is anaerobic or gas impermeable, nor does Kertz teach a separator as an element distinct from the inoculation and proliferation chambers, nor the ability to store and transport the inoculum and proliferation medium truly separately i.e., without any chance of accidental contamination of one with the other. Nor does Kertz teach or suggest that the inoculum is provided *in a form* that will be stable and viable beyond the time expected over those in conventional culture containers. For example, the present application teaches (page 10, lines 16-18) that such a form can be a freeze-dried culture. Nor does Kertz teach or suggest that the inoculation

chamber is exterior of the proliferation chamber, as recited in claim 60 as amended. Accordingly independent claim 60 is not obvious over Kertz under 35 U.S.C. §103.

(f) As to claim 61, as noted above, the fact that the inoculation chamber is exterior of the proliferation chamber allows for true separation of the inoculum and proliferation medium, in the sense that there is not even the possibility of accidental contamination of one by the other, as in there is in the apparatus of Kertz. Thus Kertz does not teach or suggest storing the inoculum and growth medium separated from one another, as recited in claim 61. Further, since Kertz does not teach a "separator" as a distinct element as recited in claim 61, there is no teaching in Kertz of opening the "separator," as recited in claim 61. Accordingly, claim 61 is not obvious over Kertz under 35 U.S.C. §103.

(g) With respect to claim 62, Kertz does not teach a distinct separator element; therefore Kertz cannot teach that such an element is sterile. Claim 62 which recites such an element therefore is not obvious over Kertz under 35 U.S.C. §103.

(h) As noted above claim 63 has been cancelled, thereby rendering this ground of rejection moot.

(i) Claim 64 recites that the apparatus is totally enclosed and hermetically sealed. The reference in the Action to Kertz page 7, second paragraph, which is a description of Fig. 7 of the reference, is respectfully not understood. The other cited portions of the reference teach heat sealing, but do not teach or suggest *hermetic* sealing. As the Kertz reference teaches the use of membranes of varying levels of gas-permeability, it is evident that the apparatus of Kertz will not be totally hermetically sealed from the environment. Hermetic sealing offers a unique advantage not taught or suggested by the Kertz reference. The apparatus of the present invention, being totally sealed, can expand under the pressure that builds up as a result of the anaerobic cultivation of the microorganisms. The apparatus of Kertz, which is designed to accommodate the inoculation of seeds, is not designed to accommodate this kind of expansion under pressure that results from use of a totally hermetically sealed chamber. Accordingly, claim 64 is not rendered obvious by Kertz under 35 U.S.C. §103.

(j) Claim 71 recites that a vial type container for the inoculum is flexible and compressible "after the septum has been opened." The inoculation chamber of Kertz

is two flat layers of plastic joined together to form a bag, which is not a vial-type container as recited in the claim. Further, Kertz does not disclose a separator as an element distinct from the walls, nor does Kertz disclose such a separator having a septum which is distinct from the walls. Accordingly claim 71 is not rendered obvious by Kertz under 35 U.S.C. §103.

(k) Claim 72 recites that the apparatus is provided with an "urging *means* for urging the inoculum into the proliferation chamber after the *septum* has been opened to inoculate the growth medium." (Emphasis added.) The Action states "KERTZ teaches an urging *function* that urges the inoculum into the proliferation chamber after the *separator* has been opened." (Emphasis added.) The urging *function* of Kertz is supplied by a flat edge such as a knife edge that is applied to the cellule. That knife edge is not part of the apparatus of Kertz. Claim 72 ultimately depends from claim 60 which recites, *inter alia*, a *unitary* apparatus. Kertz discloses an urging *function*, but does not disclose providing a *unitary* apparatus with an urging *means,* as recited in claim 72, for urging the inoculum into the proliferation chamber. Further, as noted above, Kertz does not disclose a separator as an element distinct from the walls of the chambers, and certainly does not disclose that the separator has a septum, which also is distinct from the chamber walls. Thus Kertz cannot teach or suggest that the urging means *of the apparatus* urges inoculum into the proliferation chamber after the septum has been opened, as recited in claim 72. Accordingly, claim 72 is not rendered obvious by Kertz under 35 U.S.C. §103.

(l) Claim 73 recites that there is a pressure differentiation between the inoculation and proliferating chambers which causes the inoculum to flow from the inoculation chamber to the proliferation chamber. It is helpful to understand the subject matter of claims 71, 72, and 73 within the context of the application as a whole. The present application recites three different means for causing the inoculum to flow from the inoculation chamber to the proliferation chamber, namely, compression of the vial-type container, providing an urging means, and a pressure drop between the two chambers (page 6, lines 17-22). These three means are individually recited in claims 71, 72 and 73, respectively. With respect to the method recited in claim 73, the Kertz reference teaches at page 11 that applying external pressure will cause the inoculation

chamber to break, but once it has broken the pressure between the two chambers is the same and there is no pressure difference that would cause the inoculum to flow in to the proliferation chamber, only the mechanical pushing of the flat edge against the burst chamber walls. Accordingly, claim 73 which recites the pressure difference *between the two chambers* is not rendered obvious by Kertz under 35 U.S.C. §103.

(m) Claim 74 recites a port for connecting to a dosing or application means. As explained more fully at page 10, lines 7-13, this feature relates to a means for dispensing proliferated culture *from* the apparatus. The Kertz reference discusses at page 10 paragraph 3 a means such as a tube for introducing material *to* the integument. Accordingly, this disclosure of Kertz does not render claim 74 obvious under 35 U.S.C. §103.

(n) Claim 75 recites that "the arrangement is such that pressure, which builds up in the proliferation chamber during the anaerobic cultivation of the microorganism, urges the proliferated culture through the said port." Again, this claim relates to transferring the culture *out* of the chamber *after* proliferation has taken place. The Action cites page 11 paragraph 2 – page 12 paragraph 1 of the Kertz reference, which recites means for transferring the inoculum *to* the proliferation chamber *before* proliferation can take place. Accordingly, the cited portion of the reference does not relate to the subject matter of this claim, and claim 75 is not rendered obvious by the Kertz reference under 35 U.S.C. §103.

(o) Claim 76 is non-obvious as depending from a non-obvious base claim.

(p) Claim 77 recites that the proliferation is a carboy type container. A carboy-type container is a bottle having rigid sides. The apparatus of the Kertz reference requires that the proliferation chamber have flexible sides, so that the inoculation chambers disposed therein can be compressed by an externally applied flat edge to burst the inoculation chambers and release the inoculum into the proliferation medium. Accordingly, it would not be possible to use a carboy type container in the apparatus of Kertz, and Kertz in fact teaches away from the use of a carboy type container. Accordingly, claim 77 is not rendered obvious by Kertz under 35 U.S.C. §103.

(q) Claim 78 is non-obvious as depending from a non-obvious base claim.

The rejection of claims 65-70 as obvious over Kertz (WO 90/15527) as applied above in view of Bittings (US 4,358,539) is respectfully traversed. Bittings discloses a device that is used to transfer an inoculum from a separate inoculum source, not part of the device, to an absorptive disc on an agar medium in a petri dish. The cap covering the needle is removed, the needle is inserted in and penetrates a septum on a culture bottle, and the bottle and device are inverted together to saturate the disc. Subsequently, the bottle and device are again inverted. The cap on which the disc is secured in agar can be removed from the device during incubation to inspect the status of the subculture. It is apparent that the apparatus of Bittings does not contemplate any anaerobic cultivation as recited in the present claims.

The following discussion corresponds to the lettered subparagraphs of paragraph 6 at pages 7-9 of the Office Action.

(a) Claim 65 recites the apparatus of claim 60 wherein the inoculation and proliferation chambers are connected to one another by a passage. The Action states that Bittings teaches a subculture device for transferring inoculum in which a passage (neck of a culture bottle) is provided between a culture chamber (culture media well) and inoculum chamber (culture bottle) comprising the separator (septum). Claim 65 depends from claim 60, which recites that the apparatus is a *unitary* apparatus. In Bittings, the culture bottle, culture bottle septum, and culture bottle neck all cited by the Action are not unitary with the culture chamber of the disclosed device; in fact, these features are not even illustrated in the single drawing of the Bittings reference. It would not have been obvious to incorporate the disparate features which are not even illustrated in Bittings into a unitary device, as presently claimed. Also, the device of Bittings does not allow for anaerobic proliferation of the inoculum in the culture medium. Accordingly, claim 65 is not rendered obvious under 35 U.S.C. §103 by the combination of Kertz and Bittings.

(b) Claim 66 recites the apparatus wherein the separating means is in the form of a septum. The septum on the culture bottle of Bittings does not meet this limitation, because the culture bottle of Bittings is not part of the Bittings device, and therefore is not part of a unitary apparatus, as recited in claim 60 from which claim 66 depends. Nor would it be obvious to use the septum of Bittings in the device of Kertz, because the septum requires a passage having a mouth over which the septum can be applied, while the structure of Kertz has no such passage or

mouth that can accommodate a septum. Accordingly claim 66 is not obvious over the combination of Kertz and Bittings under 35 U.S.C. §103.

(c) Claim 67 recites that the opening means is in the form of a spike for piercing the septum. Again, the opening means, the septum, and the other recited features are all part of a unitary structure. Bittings teaches that the needle is part of one structure, and the septum is affixed across a culture bottle which is a separate structure. Nor would it be feasible to incorporate a needle as used in Bittings with the structure of Kertz, which is formed from easily plastic film which can be easily pierced, because such a structure would make it much more liable that one of the chambers would be accidentally pierced by the needle and cause untimely contamination of the inoculum and proliferation media, which is exactly the problem avoided by the present invention. Accordingly, claim 67 is not rendered obvious under 35 U.S.C. §103 by Kertz in view of Bittings.

(d) Claim 68 recites that the inoculation chamber is defined by a vial-type container having a mouth which is connected to one end of the passage. The Action notes that Bittings discloses a standard culture bottle. Such a bottle does not form part of any unitary structure in the Bittings reference. The fact that such a bottle has a mouth connected to a passage does not make it obvious to use those features in a unitary structure as recited in claim 68. Nor would it be obvious to incorporate the recited features of a culture bottle into the pliable bag chambers of Kertz. Accordingly, the disclosure of a culture bottle in Bittings combined with the Kertz reference does not render claim 68 obvious under 35 U.S.C. §103.

(e) Claim 69 recites that a septum covers the mouth of the passage. The septum over the mouth of the culture bottle of Bittings does not teach the use of such a septum in a unitary structure as presently claimed, nor would it be obvious to incorporate such a septum over a passage mouth in the structure of Kertz. Accordingly, claim 69 is not rendered obvious under 35 U.S.C. §103.

(f) Claim 70 recites that the spike is mounted in the passage directed at the septum, and wherein the inoculation chamber is connected to the said one end of the passage via advancement means, the arrangement being further such that, in use, the inoculation chamber is advanced inwardly towards the spike, until the spike pierces the septum. The Action states that Bittings teaches that the spike is mounted in the passage and directed at the septum. In Bittings, the spike (needle) is mounted in the throw-away device. The passage of Bittings is the neck of

the culture bottle, which is not part of the throw-away device. Thus in Bittings the spike is not mounted in the passage, as those terms are used both in the present claims and in the Action. Accordingly, claim 70 is not obvious under 35 U.S.C. §103.

CONCLUSION

For the foregoing reasons, it is submitted that all grounds of rejection have been overcome, and a Notice of Allowance is respectfully requested.

If the Examiner is of the opinion that a telephone conference would expedite prosecution of the application, the Examiner is encouraged to contact Applicant's undersigned representative.

Respectfully submitted,

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